AMENDMENTS TO THE SPECIFICATION

At page one, after the title and before the first sentence, please insert the following paragraph:

This application is a divisional of U.S. Patent Application No. 10/133,205, filed April 26, 2002; which is a continuation of prior application No. PCT/NL00/00774, filed 26 October 2000; which claims priority from European Patent Application No. EP 99203523.0, filed 26 October 1999; all of which are hereby incorporated herein by reference.

With the paragraph starting on page 3, line 28, please amend the specification as follows:

In particular, the invention provides a method wherein stably transformed ~~tobaccoplants~~ tobacco plants with mammalian type of glycosylation are infected with modified TMV in order to produce bioactive rb TSH, rbFSH and rbFSH-R. For expressing recombinant bFSH both subunits of bFSH are inserted separately or together immediately downstream of an additional cp-promoter of TMV and subsequently checked for infectivity. For TSH, analogous methods are ...

With the paragraph starting on page 17, line 24 please amend the specification as follows:

In order to obtain a soluble FSH receptor, a fragment encoding part of its N-terminal extracellular domain was obtained by PCR. The size of the soluble receptor (293 ~~aminoacids~~ amino acids) has been chosen in order to retain all hormone interaction, and favor processing by elimination of the c-terminal ~~Cystein~~ cysteine cluster. Amplimers bearing appropriate restriction sites for subcloning the TMV vector were designed. After amplification and cloning, a synthetic

DNA encoding the FLAG epitope (sequence = DYKDDDDK (SEQ ID NO:1)) as well as a stop codon was ligated. Subcloning of the construct into the TMV vector is now in progress.

With the paragraph starting on page 19, line 6 please amend the specification as follows:

As sc-bFSH was detected almost exclusively in the soluble fraction after fractionating crude protein extracts with 100.00 x g, clearly the sc-bFSH is secreted by the plant cells into the extracellular space. Intercellular washing ~~fluit~~ fluid (IF) extractions from leaf material were carried out. As shown by Western blot analysis the sc-bFSH was clearly enriched in these IF fractions indicating a secretion of protein into the extracellular space.

With the paragraph starting on page 22, line 25 please amend the specification as follows:

In order to construct the single chain bFSH (sc-bFSH) with the carboxyl end of the b-subunit fused to the amino end of the a subunit (Sugahara et al., 1996) a gene SOEing strategy (Horton, 1993) was chosen (Fig. 1): The bFSH a subunit was amplified from the plasmid bovALPH7A-pSP64 #1 (Leung et al., 1987) using the primers FSH-F 5'-GGA AAT CAA AGA ATT TCC TGA TGG AGA GTT TAC AAT GCA G-3' (SEQ ID NO:2), containing 13 bp of the b subunit's carboxyl end, and Nsi-STOP 5'-AGC TAT GCA TCT ATT AGG ATT TGT GAT AAT AAC A-3' (SEQ ID NO:3). The bFSH b subunit was amplified from the plasmid Bov FSHbeta pGEM3 (Maurer and Beck, 1986) using the primers FSH-A 5'-ATA TGA GTC GAC ATG AAG TCT GTC CAG TTC-3' (SEQ ID NO:4) and FSH-E 5'-CTC CAT CAG GAA ATT CTT TGA TTT CCC TGA AGG AGC AGT A-3' (SEQ ID NO:5), the latter including 13 bp of the a 5'-end. The resulting 2 fragments which contain a 26 bp overlapping region were combined in 5 PCR extension cycles with an annealing temperature of 45 °C. Subsequently, this

overlap PCR product was amplified by PCR using the primers FSH-A and Nsi-STOP. Following SaiI / NsiI digestion, this fragment was ligated to SalI I / PstI restricted TMV based expression vector p4GD-PL (Casper and Holt, 1996), resulting in the construct p4GD-sc-bFSH. This construct was used for all expression experiments.

With the paragraph starting on page 23, line 26 please amend the specification as follows:

12-16 dpi the replicative stability of the hybrid TMV RNA - genome derived from p4GD-sc-bFSH was investigated. Total RNA from systemically infected leaves was prepared using TriReagent (Molecular Research Centre, Inc.) and cDNA synthesis (reverse transcription) was performed using the TMV (p4GD-PL) specific reverse primer p4GD-RV 5'-TTT TTC CCT TTT TTG TTT TCC G-3' (SEQ ID NO:6) located downstream the multiple cloning site. Using p4GD-RV and the TMV specific forward primer p4GD-FW 5'- GAT GAT GAT TCG GAG GCT ACT-3' (SEQ ID NO:7) which anneals upstream of the multiple cloning site, a specific RT-PCR...

With the paragraph starting on page 25, line 26 please amend the specification as follows:

Protein extracts prepared as described above were electrophoresed on 12.5% SDS-polyacrylamide gels under reducing conditions (Lämmli, 1970). Following electroblotting onto nitrocellulose (Amersham Life Science Ltd., U.K.), the blots were blocked with 5% non-fat dry milk in TBS containing 0,1% Tween 20 (Sigma, MI, USA). The primary antibody was an anti-human FSH b-subunit (R812~~, reference!~~) rabbit polyclonal antiserum diluted to 1:2500 in TBS

containing 0,1% Tween (TTBS) and 1% BSA (Sigma, MI, USA). As secondary antibody, an anti-rabbit IgG goat polyclonal ~~antiserum horde radish~~ antiserum-horseradish peroxidase . . .

With the paragraph starting on page 28, line 24 please amend the specification as follows:

IF - extracts from N. *benthamiana* plants infected by p4GD-sc-bFSH or p4GD-PL (negative control) were diluted in GMEM-S medium without calf serum in a final volume of 0.2 ml as indicated in fig. ~~8, A~~ 6. These extract dilutions were incubated on CHO cell layers expressing the porcine FSH receptor (Abdennebi *et al.,* 1999) for ~~1h 30~~ one hour and 30 minutes at 37°C. Known concentrations of pituitary bFSH were applied to cells in the same conditions (see fig. [[8, B]] 6). cAMP levels in supernatants were determined using a specific RIA (NEN-Dupont de Nemours, Les Ulis, France). All assays were performed in duplicate and repeated twice.

With the paragraph starting on page 37, line 7 please amend the specification as follows:

Evidently, the N-glycans present on sc-bFSH exhibit considerable structural aberration from its native counterpart, pituitary bFSH (Baenzinger and Green, 1988). As anticipated from known plant N-glycan structures, no N-glycans of the mammalian complex-type were found, neither b1,4 linked galactose nor terminal sialic acid. b(1,2) xylose and core a(1,3) fucose have never been found in mammal cells and they are considered potentially immunogenic structures (Wilson *et al.,* 1988; Kurosoka *et al.,* 1991; Faye *et al.,* 1993[[??]]). Although so far no negative effect has been reported for plantibodies applied to mammals which might result from these sugars, no long term studies are available.

At page 39, before "Figure legends," please insert the following subheading:

BRIEF DESCRIPTION OF THE DRAWINGS

With the paragraph starting on page 42, line 28 please amend the specification as follows:

Ma, J.K., Hiatt, A., Hein, Ml., Vine, N.D., Wang, F., Stabila, P., van Dolleweerd, C., Mostov, K. and Lehner, T. (1995). Generation and assembly of secretory antibodies in plants ~~see comments.~~ Science 268, 716-9.